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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,687	11/14/2001	David Botstein	P2730P1C11	4943

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,687	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The appeal brief of 13 June 2007 has been received and considered. Upon further consideration, finality of the previous Office Action (mailed 13 October 2006) is *withdrawn* solely to clarify the issues for appeal, and to provide Applicant with an opportunity to respond accordingly.

35 U.S.C. §§ 101 and 112, First Paragraph - Utility

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

A portion of the basis for these rejections is withdrawn. Specifically, the examiner no longer asserts that **mRNA levels** are not predictive of polypeptide levels. Therefore, the following references are no longer being relied upon to support the rejections: Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., Nagaraja et al., Waghray et al., Sagnaliev et al., Lilley et al., Wildsmith et al., King et al., Bork et al., Celis et al., and Madoz-Gurpide et al. The following references cited and discussed by Applicant pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher et al., Alberts and Lewin, Meric et al., Zhigang et al., Wang et al., Munaut et al. The basis of the maintained rejections is solely that **gene amplification levels** are not predictive of mRNA or polypeptide levels.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to isolated native sequence polypeptides comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 194 with or without its signal peptide, or the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209792, wherein the nucleic acid encoding said polypeptide is amplified in colon cell carcinomas. It is noted that the phrase "wherein the nucleic acid encoding said polypeptide is amplified in colon cell carcinomas" is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic acid. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity. Claims are also presented to chimeric

proteins comprising the aforementioned polypeptides. The specification discloses the polypeptide of SEQ ID NO: 194, also known as PRO1009. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief (received 13 June 2007), p. 4, beginning of arguments.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1009 had a ΔCt value of at least 1.0 for twelve out of sixteen colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

First, there are several problems with the data provided in this example. The art

recognizes that colon epithelium is can be aneuploid without the presence of cancer. For example, pre-malignant lesions and ulcerative colitis have been associated with aneuploidy. See Fleischhacker et al. (1995, Modern Pathology 8:360-365), especially p. 360, 1st paragraph of introduction. The gene amplification assay in the instant specification does not provide a comparison between the colon tumor samples and normal colon epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1009 is amplified in cancerous colon epithelium more than in damaged (non-cancerous) colon epithelium. One skilled in the art would not conclude that PRO1009 is a diagnostic probe for colon cancer unless it is clear that PRO1009 is amplified to a clearly greater extent in true colon tumor tissue relative to non-cancerous colon epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, the data have no bearing on the utility of the claimed PRO1009 *polypeptides and polypeptide variants*. In order for PRO1009 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1009 mRNA or PRO1009 polypeptide levels in colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

The *general* concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12) also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) teach a general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a***

number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." (emphasis added). The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1009 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and

transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidene for PRO1009.

Therefore, data pertaining to PRO1009 genomic DNA do not indicate anything significant regarding the claimed PRO1009 polypeptides and variants thereof. The data do not support the specification's assertion that PRO1009 polypeptides and variants thereof can be used as cancer diagnostic agents. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1009 polypeptides and variants thereof are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1009 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1009 **polypeptides and variants thereof** as diagnostic markers and therapeutic targets are simply starting points for further research and

investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Fleischhacker et al., Sen, Hittelman, Godbout et al., and Li et al., all of which are of record and have been previously discussed), the rejections are properly maintained.

Applicant's arguments pertaining to the remaining issues (Appeal Brief, 13 June 2007) have been fully considered but are not found to be persuasive for the following reasons.

Applicant's detailed arguments begin at p. 7 of the appeal brief. Applicant begins with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at p. 11 of the brief, Applicant reviews Example 170, and refers to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 04 August 2005 is insufficient to overcome the rejection of claims 119-

126 and 129-131 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.085 to 4.287-fold amplification of the gene encoding PRO1009 in twelve colon tumors is significant, and whether such data have any relevance to the claimed subject matter, i.e., PRO1009 polypeptides and variants thereof. The significance can be questioned based on the strength of opposing evidence. In the instant case, the control used was not a matched non-tumor colon sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Fleischhacker et al., Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides and variants thereof have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins or variants thereof are also found at increased levels in

cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

Applicant argues that the PRO1009 gene is an important diagnostic marker to identify colon cancer or for diagnosing individuals at risk for colon cancer. This has been fully considered but is not found to be persuasive. First, while the argument is pertinent with regard to PRO1009 genes, it does not address the claimed subject matter, which is PRO1009 polypeptides and variants thereof. It is important to clarify that no evidence has been brought forward to establish that the PRO1009 **polypeptide** is amplified in any lung tumors. Furthermore, nowhere does the specification assert a utility for the claimed PRO1009 polypeptides and variants thereof as being useful to diagnose subjects *at risk for* developing colon cancer, and therefore this argument also is not persuasive. Finally, even if it could be established that PRO1009 gene is significantly amplified in colon carcinomas compared to healthy colon tissue, it does not follow that PRO1009 polypeptide and variants thereof would also be over-expressed and thus useful as a cancer diagnostic molecule, for reasons discussed extensively on the record.

Applicant relies on Orntoft et al., Hyman et al., and Pollack et al. as evidence that gene amplification increases mRNA expression in general. This has been fully considered but is not found to be persuasive. Orntoft et al. used the CGH method to look at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. However, Orntoft et al. do not look at gene amplification, mRNA levels and polypeptide levels from a single

gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1009 in the instant specification. That is, it is not clear whether or not PRO1009 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al. does not support utility and enablement of the claimed polypeptides and variants. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides and variants. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Equally importantly, none of the papers address whether or not variants of a specific polypeptide are overexpressed in cancer. Thus, at the very least, these pieces of evidence are not commensurate in scope with the claims, which encompass polypeptides having only 80% sequence identity to the mature portion of PRO1009

polypeptide of SEQ ID NO: 194. Significant further research would be required to identify which PRO1009 polypeptides and variants, *if* any, are overexpressed in colon cancer compared to healthy colon tissue. Accordingly, the specification's assertions that the claimed PRO1009 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

At p. 13, Applicant criticizes Pennica et al. and Konopka et al. as not being specific to PRO1009, instead as being specific to other genes, and not establishing a general trend. This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica and Konopka constitute evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect. Finally, Fleischhacker et al., Sen, and Hittelman constitute evidence that, in general, non-cancerous epithelial tissues are frequently aneuploidy, and thus an increase in genomic DNA is not diagnostic of cancer.

At p. 18, Applicant again argues that the gene amplification data establish a credible, specific, and substantial patentable utility for the PRO1009 polypeptide. Applicant points to the assertion in the specification that gene amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention and diagnostic determination of certain cancers. Applicant argues that ample evidence has been submitted to show that, in general, if a gene is amplified in cancer, then it is more likely than not that the encoded

protein is also overexpressed. Specifically, Applicant refers to Orntoft et al., Hyman et al., and Pollack et al. This has been fully considered but is not found to be persuasive for the reasons set forth above regarding these references. See pp. 11-12 of the instant action.

Applicant refers to the Polakis declaration of 29 June 2006. The Polakis declaration under 37 CFR 1.132 filed 29 June 2006 is insufficient to overcome the rejection of claims 119-126 and 129-131 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because the declaration focuses on the question of whether or not mRNA levels are predictive of protein levels. As explained above, the examiner is no longer arguing this point. Since the Polakis declaration does not address the question of whether or not amplified genomic DNA is predictive of increased polypeptide levels, it is no longer considered pertinent to the rejection.

Applicant argues that the sale of gene chips is indicative of the research community's opinion that mRNA levels are predictive of protein levels. This has been fully considered but is not found to be persuasive for two reasons. First, evidence of commercial success is irrelevant to utility and enablement. Second, this does not address whether or not genomic DNA levels are predictive of protein levels.

At pp. 20-21, Applicant concludes that, based on the asserted utility for PRO1009 in the diagnosis of selected colon tumors, the reduction to practice of the PRO1009 protein sequence, the disclosure of methods for making polypeptides and chimeric polypeptides comprising PRO1009 and antibodies that bind PRO1009, and example 170 regarding the gene amplification assay, one skilled in the art would know exactly

how to make and use the claimed polypeptides for diagnosis of lung carcinoma without undue experimentation. Applicant urges that, in general, DNA amplification correlates with increased expression of the encoded protein. Applicant argues that the specification shows significant amplification in three different lung primary tumors, evidence in the form of publications has been submitted to establish that a general DNA/mRNA/protein correlation exists, and declarations from experts have been provided to further support Applicant's position. Applicant concludes that the utility of the claimed PRO1009 polypeptides has been achieved. Applicant stresses that absolute certainty is not required, and that it has been established that it is more likely than not that PRO1009 polypeptides are overexpressed in certain lung carcinomas. This has been fully considered but is not found to be persuasive for the following reasons. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged colon epithelium (evidenced by Fleischhacker et al.). Evidence has also been brought forth that aneuploidy is characteristic of other damaged epithelial tissues (Sen, Hittelman). Gene amplification publications used matched tissue controls, unlike applicant (Pennica et al., Konopka et al., Godbout et al., Li et al.). Contrary to Applicant's assertion, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Konopka et al., Godbout et al., Hyman et al., and Li et al. Finally, a declaration setting forth the expert opinion of Dr. Ashkenazi (received 18 June 2004) contradicts the assertion of utility in the specification, wherein the specification indicates that gene

amplification is associated with protein overexpression but Dr. Ashkenazi indicates that this is not always the case. Since significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1009 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. In the absence of information regarding whether or not PRO1009 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1009 **polypeptides and variants thereof** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Hanna and Mornin (1999, Pathology Associates Medical Laboratories) also supports the instant rejections. Hanna and Mornin provide another important example of a lack of correlation between gene amplification and mRNA/protein overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin provide evidence that the level of protein expression must be tested empirically

to determine whether or not the protein can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the protein level of PRO1009 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed proteins is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial. Regarding Applicant's argument that lack of protein overexpression leads to more effective categorization and treatments, the specification provides no assertion that the claimed PRO1009 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO1009. Therefore, significant further research would be required before such a utility were deemed substantial.

Finally, it is noted that the claims are extremely broad, in that they are not limited to PRO1009 polypeptide alone, but rather to variants that comprise sequences that are only 80% identical to the mature portion of the PRO1009 protein of SEQ ID NO: 194. None of the evidence of record is commensurate in scope with these claims, since none of the evidence addresses utility or enablement of variants.

35 U.S.C. § 112, First Paragraph – Written Description

Claims 119-123, 130, and 131 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record.

Applicant's arguments (pp. 21-26, Appeal Brief, 13 June 2007) have been fully considered but are not found to be persuasive.

From p. 21 to p. 22, Applicant reviews the legal requirements for written description, with which the examiner takes no issue.

At pp. 22-23, Applicant argues that the specification evidences the reduction to practice of SEQ ID NO: 194. Applicant urges that the specification provides support for "native sequences" and methods of determining percent identity. Applicant argues that the specification provides detailed guidance as to changes that can be made to a PRO polypeptide without adversely affecting activity. Applicant concludes that the skilled artisan would be able to determine if a variant PRO polypeptide falls within the parameters of the claimed invention. This has been fully considered but is not found to be persuasive. There is no doubt that there is adequate written description for SEQ ID NO: 194. However, the guidance to which applicant refers pertaining to variants is the type of broad-brush guidance that can be applied to variants of any polypeptide, and as such is tantamount to an invitation to experiment to find previously non-described polypeptides that may fall within the boundaries of the claims. As was found in *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

Applicant argues that the claims recite a functional requirement that the nucleic acids encoding the polypeptides are amplified in colon tumors. Applicant further argues

that the specification provides guidance regarding how to screen for such. This has been fully considered but is not found to be persuasive. Whether or not a nucleic acid is amplified in a specific tissue is not a function of the polypeptide. Nucleic acid amplification is a characteristic of the nucleic acid, but is not a function. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity.

Applicant refers to arguments presented regarding the 35 U.S.C. §§ 101 and 112, first paragraph, utility and enablement issues. Applicant urges that gene amplification correlates with increased polypeptide expression. This has been fully considered but is not found to be persuasive for the reasons set forth above.

Applicant argues that whether or not the polypeptide is overexpressed in tumor tissues is irrelevant to the issue of written description. Applicant contends that the claims require that the polypeptides be encoded by polynucleotides that are amplified in colon tumors, and the specification provides methods for screening for same. This has been fully considered but is not found to be persuasive for two reasons. First, the amplification pattern of a gene encoding a particular polypeptide imparts no distinguishing characteristic on the encoded polypeptide. Second, a statement that something is part of the invention and reference to a potential method of making or screening for it does not constitute adequate written description. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant argues that the *Fiers* and *Fiddes* cases do not apply to the instant claims since the subject matter at issue in *Fiers* and *Fiddes* was polynucleotides, not polypeptides. This has been fully considered but is not found to be persuasive, since both polynucleotides and polypeptides are naturally occurring biological molecules. Conception of a polypeptide also requires a precise definition, such as by structure, formula, chemical name, or physical properties.

Regarding *Fiddes v. Baird*, Applicant further argues that the distinguishing fact of the case pertained to *Baird's* failure to disclose naturally occurring mammalian gene sequences (only theoretical bovine DNA sequences were disclosed). Applicant urges that the instant fact pattern can be distinguished since SEQ ID NO: 194 is fully disclosed, and guidance is provided to determine whether or not a variant polypeptide falls within the scope of the claims. This has been fully considered but is not found to be persuasive. In the instant case, only SEQ ID NO: 194 is fully described. No sequences, naturally occurring or theoretical, are provided in the instant specification for variant PRO1009 polypeptides that are encoded by nucleic acids that are amplified in colon tumors. Therefore, applying the findings of *Fiddes v. Baird* to the instant application, the only conclusion can be that there is no written description for the variants.

Applicant discusses the *Enzo* case, reviewing the court's finding that the written description requirement can be met by showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics...*i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics

when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Applicant urges that the instant claims meet the *Enzo* standard in that the polypeptides are described by function and structure, the combination of which may suffice to describe a claimed genus. This has been fully considered but is not found to be persuasive because the instantly claimed polypeptides are not described functionally. As discussed above, whether or not a gene is amplified in a particular tissue does not impart any distinguishing feature, function, or characteristic on the encoded polypeptide. Therefore, only a percent identity to a full length sequence is recited. There is not even a recitation of which part of the sequence should be conserved, nor is there guidance in the specification beyond the general instruction to try conservative substitutions and screen. Such an approach can be used for any polypeptide and is not specific to PRO1009. As such, it is not specific written description, but an invitation to experiment. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states: "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement

"by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966. In the instant case, no variant sequences meeting the claim limitations are disclosed in the specification. Thus, the instant genus claims are not adequately supported, since a single species is not representative of the genus.

For all of these reasons, the written description rejection is maintained.

Conclusion

No claims are allowed.

No new rejections have been made. THUS, THIS ACTION IS MADE FINAL. However, since new publications have been cited to support the maintained rejections, Applicant is assured that any new evidence specifically addressing Hittelman, Sen, or Fleischhacker et al. will be entered after final and given full consideration. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646